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1: Am J Pathol. 1998 Aug;153(2):395-403.

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Expression of the vascular endothelial growth factor C receptor VEGFR-3 in lymphatic endothelium of the skin and in vascular tumors.

Lymboussaki A, Partanen TA, Olofsson B, Thomas-Crusells J, Fletcher CD, de Waal RM, Kaipainen A, Alitalo K.

Department of Pathology, Haartman Institute, University of Helsinki, Finland.

It is difficult to identify lymph vessels in tissue sections by histochemical staining, and thus a specific marker for lymphatic endothelial cells would be more practical in histopathological diagnostics. Here we have applied a specific antigenic marker for lymphatic endothelial cells in the human skin, the vascular endothelial growth factor receptor-3 (VEGFR-3), and show that it identifies a distinct vessel population both in fetal and adult skin, which has properties of lymphatic vessels. The expression of VEGFR-3 was studied in normal human skin by *in situ* hybridization, iodinated ligand binding, and immunohistochemistry. A subset of developing vessels expressed the VEGFR-3 mRNA in fetal skin as shown by *in situ* hybridization and radioiodinated vascular endothelial growth factor (VEGF)-C bound selectively to a subset of vessels in adult skin that had morphological characteristics of lymphatic vessels. Monoclonal antibodies against the extracellular domain of VEGFR-3 stained specifically endothelial cells of dermal lymph vessels, in contrast to PAL-E antibodies, which stained only blood vessel endothelia. In addition, staining for VEGFR-3 was strongly positive in the endothelium of cutaneous lymphangiomas, but staining of endothelial cells in cutaneous hemangiomas was weaker. These results

establish the utility of anti-VEGFR-3 antibodies in the identification of lymphovascular channels in the skin and in the differential diagnosis of skin lesions involving lymphatic or blood vascular endothelium.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 9708800 [PubMed - indexed for MEDLINE]

PMCID: PMC1852985

 2: Exp Eye Res. 1998 Jun;66(6):747-54.

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Ciliary muscle capillaries have blood-tissue barrier characteristics.

Schlingemann RO, Hofman P, Klooster J, Blaauwgeers HG, Van der Gaag R, Vrensen GF.

Department of Ophthalmology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.

It was determined whether the capillaries in the ciliary muscle are of the blood-tissue barrier or of the permeable non-barrier type. Ciliary body and iris of normal human and animal eyes were examined by electron microscopy and by immunohistochemical staining with a panel of antibodies recognizing endothelial blood-brain barrier markers. In addition, horseradish peroxidase (HRP) tracer studies of the anterior segment were carried out in rabbits. Our results demonstrated that the capillary endothelium in human and rabbit ciliary muscle has few luminal pinocytotic vesicles and a morphological aspect suggesting the presence of tight junctions. Ciliary muscle and iris capillaries stained positive for the blood-brain barrier markers Glucose-Transporter-1 and P-Glycoprotein, while staining for the PAL-E antigen and the transferrin receptor was absent. In the rabbit ciliary muscle, vascular leakage of exogenous HRP tracer was absent. It was concluded that this functional barrier and the observed phenotype of ciliary muscle capillaries are consistent with a blood-tissue barrier function similar to that of the iris microvasculature. Copyright 1998 Academic Press.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 9657907 [PubMed - indexed for MEDLINE]

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Expression of endoglin in the transition between psoriatic uninvolved and involved skin.

van de Kerkhof PC, Rulo HF, van Pelt JP, van Vlijmen-Willems IM, De Jong EM.

Department of Dermatology, University Hospital Nijmegen, The Netherlands.

Endoglin is a glycoprotein which is predominantly expressed on endothelial cells. It is upregulated under inflammatory conditions as well as in skin lesions where endothelial cell proliferation occurs. Endoglin has the capacity to bind transforming growth factor beta (TGF-beta) and can reduce the bioavailability of TGF-beta. TGF-beta has a growth-inhibiting effect on keratinocytes and a restraining influence on the extravasation of peripheral white blood cells. In order to find out how endoglin is expressed in the margin zone of psoriatic plaques and how it correlates with the appearance of an inflammatory infiltrate, punch biopsies were taken from the margin zone of actively spreading psoriatic plaques in 8 patients. Indirect immunoperoxidase staining was performed using PAL-E (vascular endothelium), PN-E2 (anti-endoglin) and T11 (T-lymphocytes). In all patients it was found that the appearance of parakeratosis correlated with a clear increase of PN-E2 expression. PAL-E and PN-E2 expression was assessed, using a 5-point scale. Thus a tendency to decreased PN-E2 expression in uninvolved skin compared to PAL-E expression was found within the margin zone (1.6 +/- 0.4 and 2.2 +/- 0.4, respectively), whereas in involved skin PN-E2 expression and PAL-E expression were in agreement (2.6 +/- 0.5 and 2.6 +/- 0.5 respectively), suggesting that in the overt plaque all endothelium is in a so-called activated state. Also correlating with PN-E2 expression was the appearance of a huge dermal lymphocytic infiltrate and epidermal T-lymphocytic expression. The present study lends further support for a permissive role of endoglin expression in the development of the psoriatic lesion.

PMID: 9498020 [PubMed - indexed for MEDLINE]

□ 4: Lab Invest. 1997 Oct;77(4):345-55.

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Expression of matrix metalloprotease-9 in vascular pericytes in human breast cancer.

Nielsen BS, Sehested M, Kjeldsen L, Borregaard N, Rygaard J, Dano K.

Department of Pathology, Rigshospitalet, Copenhagen, Denmark.

Matrix metalloprotease-9 (MMP-9; 92-kd type IV collagenase,

gelatinase B) is regarded as important for degradation of the basement membrane and extracellular matrix during cancer invasion and other tissue-remodeling events. Expression of MMP-9 was analyzed in 22 cases of human ductal breast cancer by immunohistochemistry and in 8 of these cases also by *in situ* hybridization. For immunohistochemistry we used affinity-purified polyclonal antibodies as well as a MMP-9-specific monoclonal antibody (clone 6-6B). Three different stromal cell types with a positive MMP-9 immunoreaction were identified morphologically: neutrophils and macrophage-like cells in all cases and vascular cells in 16 of 22 cases. Double immunofluorescence with antibodies to CD68 conclusively demonstrated MMP-9 expression in macrophages. To identify the positive vascular cells, we employed antibodies to von Willebrand factor and PAL-E for identification of endothelial cells, high molecular weight melanoma-associated antigen for pericytes, and alpha-smooth muscle actin for vascular smooth muscle cells. Using conventional and confocal double immunofluorescence microscopy, colocalization of MMP-9 was seen with high molecular weight melanoma-associated antigen, the pericyte marker, whereas little or no coexpression was seen with alpha-smooth muscle actin. Virtually no coexpression was seen with the endothelial cell markers PAL-E and von Willebrand factor. *In situ* hybridization showed that MMP-9 mRNA colocalized with MMP-9 immunoreactivity in macrophages and vascular structures, whereas no MMP-9 mRNA was detected in neutrophils. No MMP-9 immunostaining or *in situ* hybridization signal was detected in cancer cells in any of the cases. Based on these results, it is concluded that MMP-9 in human breast cancer is located in tumor-infiltrating stromal cells, including neutrophils, macrophages, and vascular pericytes, and that the latter two cell types also produce this metalloprotease. We suggest that the MMP-9 produced in pericytes may play a role in extracellular matrix degradation during tumor angiogenesis.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 9354769 [PubMed - indexed for MEDLINE]

5: Hepatology. 1997 Aug;26(2):407-15.

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Immunohistochemical studies on endothelial cell phenotype in hepatocellular carcinoma.

Nakamura S, Muro H, Suzuki S, Sakaguchi T, Konno H, Baba S, Syed AS.

Second Department of Surgery, Hamamatsu University School of Medicine, Handa-cho, Hamamatsu-city, Japan.

To examine the phenotype of the sinusoidal endothelial cells (SECs) surrounding tumor cells and the process of capillarization in hepatocellular carcinoma (HCC), 51 primary HCCs, 4 adrenal metastases, and 3 portal tumor thrombi were immunohistochemically stained with monoclonal antibodies (MAbs) for CD4, CD14 (lipopolysaccharide-binding protein complex receptors), and CD32 (Fc gamma receptor II), which are specifically found on the SECs in normal liver, but not on ordinary vascular endothelial cells (ECs). Immunostaining was also performed for CD36 (thrombospondin receptors), EN4 antigen (Ag) (a pan-vascular endothelial cell Ag), PAL-E Ag (a venous and capillary EC Ag), factor VIII-related Ag (FVIIIRAg), and laminin. MAb 25F9, which identifies macrophages, was simultaneously used with the other MAbs to distinguish macrophages from SECs in HCCs (HCC SECs). CD4, CD14, and/or CD32 were found on HCC SECs only in 12 well-differentiated primary HCCs showing a thin trabecular or pseudoglandular tumor cell arrangement. These 12 tumors were smaller than those without CD4-, CD14-, and/or CD32-positive SECs ($P < .05$). Among them, 7, 5, and 11 tumors were negative or only partially positive for laminin, PAL-E Ag, and FVIIIRAg, respectively. Staining for laminin and PAL-E Ag showed an inverse relationship to the expression of CD4, CD14, and CD32 on HCC SECs and the tumor differentiation. In conclusion, the phenotypes of the SECs in early and well-differentiated HCC are thought to be similar to those of the SECs in normal liver. With progressing tumor dedifferentiation the HCC SECs lose the phenotypes peculiar to liver SECs and acquire the characteristics of capillary ECs, though both types of phenotypical change occur independently of each other.

PMID: 9252152 [PubMed - indexed for MEDLINE]

■ 6: Ophthalmic Res. 1997;29(3):130-8.

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Vascular expression of endothelial antigen PAL-E indicates absence of blood-ocular barriers in the normal eye.

Schlingemann RO, Hofman P, Anderson L, Troost D, van der Gaag R.

Department of Ophthalmology, University of Amsterdam, The Netherlands.

The endothelium-specific antigen PAL-E is expressed in capillaries and veins throughout the body with the exception of the brain, where the antigen is absent from anatomical sites with a patent blood-brain barrier. In this study we determined vascular endothelial staining for PAL-E in the normal eye in relation to the ocular blood-tissue barriers. Immunohistochemical staining of frozen tissue sections of eyes from

22 cornea donors and a number of normal animal autopsy eyes was performed for the PAL-E antigen and the blood-brain barrier marker glucose transporter 1. In normal human and animal eyes, endothelial PAL-E staining was absent from the microvasculature in iris, ciliary muscle, optic nerve and retina. In a few normal human eyes, some weakly stained capillaries were observed in the retina and nerve fiber layer, mostly in the peripapillary area. Marked staining of capillaries and venules with PAL-E was observed in the conjunctiva, episclera, sclera, ciliary processes, choriocapillaris and optic nerve head. In general, the endothelial antigen PAL-E is absent from microvessels involved in the blood-ocular and the blood-retinal barriers. PAL-E may therefore be a useful marker to identify pathological breakdown of blood-ocular barriers.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 9211465 [PubMed - indexed for MEDLINE]

7: Exp Cell Res. 1996 Dec 15;229(2):336-49.

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Recruitment of type I collagen producing cells from the microvasculature in vitro.

Ivarsson M, Sundberg C, Farrokhnia N, Pertoft H, Rubin K, Gerdin B.

Department of Medical and Physiological Chemistry, Uppsala University, Uppsala, S-751 23, Sweden. Rubin@medkem.uu.se

We have previously suggested that microvascular pericytes can differentiate into fibroblast-like, type I collagen-producing cells during excessive dermal scarring in vivo (Sundberg, C., Ivarsson, M., Gerdin, B., and Rubin, K., Lab. Invest. 74, 454-468, 1996). Here we have investigated to what extent pericytes derived from microvessels of full-term human placenta exhibited this capacity in vitro. Vascular fragments of human term placenta were isolated by enzymatic digestion and separation in Percoll. Their microvascular origin was ascertained by confocal microscopy using antibodies specific for endothelial cells (PAL-E) and pericytes (high-molecular-weight-melanoma-associated antigen). When vascular fragments were cultured in vitro, large cells with irregular edges migrated out from the fragments. After 4-6 days in culture, these cells started to proliferate and reached near confluence after approximately 8 days. The cultures were not overgrown by clones of cells with a high proliferative capacity, as demonstrated by cell membrane fluorescence staining and Ki67 expression. Expression of PAL-E, high-molecular-weight-melanoma-associated antigen, smooth muscle alpha-actin, desmin and

collagen synthesis (prolyl-4-hydroxylase and type I procollagen, as well as collagen pro-alpha1(I) mRNA) were followed during a culture period of 8 days. The cells were PAL-E negative but expressed high-molecular-weight-melanoma-associated antigen, smooth muscle alpha-actin, and desmin. Based on morphology and expression of the various markers, the outgrowing cells were identified as pericytes. With time in culture the cells decreased their expression of all these markers and increased their expression of prolyl-4-hydroxylase, type I procollagen, and collagen pro-alpha1(I) mRNA. Metabolic labeling and SDS-PAGE analysis of labeled proteins revealed that type I collagen was the major collagen species synthesized in the cultures. Our results support the hypotheses that pericytes can leave the vasculature and differentiate into collagen-producing cells and that cultured "fibroblasts" are derived from pericytes.

Publication Types:

- In Vitro
- Research Support, Non-U.S. Gov't

PMID: 8986617 [PubMed - indexed for MEDLINE]

■ 8: *Vet Immunol Immunopathol*, 1996 Sep;53(1-2):115-27.

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Immunohistochemical demonstration of cellular antigens of the cat defined by anti-human antibodies.

Joling P, Broekhuizen R, de Weger RA, Rottier PJ, Egberink H.

Department of Pathology, University Hospital, Utrecht, Netherlands.
p.joling@labazu.nl

A panel of monoclonal antibodies (mAb) and some polyclonal rabbit sera directed against human antigens were studied on cryostat tissue sections of three cats using immunohistochemistry. Reactivity of the antibodies was tested on feline tonsil, intestine, thymus, lymph node and spleen with a three-step immunoperoxidase technique and compared with reactions on human thymus, lymph node and spleen. From a total of 95 antibodies, 28 gave reactivity comparable with that in human tissues. The remaining antibodies gave none or miscellaneous results. The positive reactions in the cat included antibodies directed to adhesion molecules (VLA-2 and VLA-4), to natural killer (NK) cells (CD56, CD57 and NCAM), to complement receptor CR1, to proliferation marker Ki-67 (MIB-1), to endothelial antigens (EN-4, PAL-E and von Willebrand factor) and to structural proteins like vimentin, desmin, collagen type IV and cytokeratin. The identification of these cross-reacting antibodies extends the spectrum of immunological reagents that are now available for the cat, and will thus contribute to the study of the feline immune system.

□ 9: Eur J Cardiothorac Surg, 1996;10(8):676-83.

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Vascular adhesion molecules and immunogenicity in blood vessels used as coronary artery bypass grafts.

Chester AH, Borland JA, Taylor PM, Rose ML, Yacoub MH.

Department of Cardiothoracic Surgery, Imperial College of Science, Technology and Medicine, National Heart and Lung Institute, Harefield Hospital, Middlesex, UK.

OBJECTIVE: The performance of coronary bypass grafts can be affected by a variety of circulating cell types. The initial event in any biological effect of such cells is adherence to the vascular endothelium prior to migration into the perivascular space. We aimed to investigate the expression of molecules that regulate cell adhesion in blood vessels employed as bypass conduits. **METHODS:** Segments of human saphenous vein, internal mammary artery, gastroepiploic artery and inferior epigastric artery were stained using specific monoclonal antibodies against the endothelial workers EN-4, Pal-E, von Willebrand factor small (vWF), and the cell adhesion molecules platelet-endothelium cell adhesion molecule (PECAM), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin, the leucocyte marker (CD45) and major histocompatibility complex (MHC) class I and II antigens, with visualisation by ABC immunoperoxidase method. **RESULTS:** All vessels had a strong expression of the endothelial specific antigens EN4, vWF, and PECAM as well as MHC class I. However, there was less expression of Pal-E, ICAM-1, E-Selectin and of the DR determinant of MHC class II. VCAM-1, DP and DQ determinants of MHC class II were expressed to a weaker extent. There were no marked differences in the expression of all the molecules examined between the four vessel types. **CONCLUSION:** Thus vessels used as bypass grafts are immunogenic and possess the potential to attract and interact with blood elements. Definition of the molecules responsible could offer opportunities for modulating the response to such interactions.

PMID: 8875178 [PubMed - indexed for MEDLINE]

□ 10: J Invest Dermatol, 1996 Jan;106(1):135-40.

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Phenotype of normal cutaneous microvasculature.

Immunoelectron microscopic observations with emphasis on the differences between blood vessels and lymphatics.

Erhard H, Rietyeld FJ, Bröcker EB, de Waal RM, Ruiter DJ.

Department of Pathology, University of Nijmegen, The Netherlands.

The lymphatic system has been poorly characterized in comparison to the blood vessels. We investigated the expression of microvasculature markers in cutaneous lymphatics and blood microvessels in normal skin. Scrotal skin was chosen because of its high density of both types of microvessels. A pre-embedding peroxidase-conjugated immunoelectron microscopy technique was used, allowing both the visualization of the lymph and blood vessels and their immunohistochemical staining. The markers studied included endothelial antigens (recognized by PAL-E, EN-4, and von Willebrand factor/factor VIII-related antigen), structural molecules of the vascular wall (alpha-smooth muscle actin, heparan sulfate proteoglycan, collagen type IV), and adhesion molecules (endothelial leukocyte adhesion molecule-1 [E-selectin], intercellular adhesion molecule-1 [ICAM-1], platelet endothelial adhesion molecule-1 [PECAM-1], vascular cell adhesion molecule-1 [VCAM-1]). It is shown that lymphatics of normal skin are phenotypically different from blood microvasculature, only weakly expressing endothelial markers (EN-4+, von Willebrand factor/factor VIII-related antigen +/-, PAL-E-), mural markers (alpha-smooth muscle actin-, heparan sulfate proteoglycan-, collagen type IV+) and do not express the studied adhesion molecules except PE-CAM-1 (E-selectin-, ICAM-1-, PECAM-1+, VCAM-1-). The results were substantiated by a double-labeling immunoelectron microscopic technique, which facilitates detection and assessment of microvascular segments. By this technique, collagen type IV, recognized by a peroxidase-labeled 2nd antibody, stains the basal lamina by a linear pattern, whereas a second optional epitope is visualized as grains by a silver-enhanced ultra-small gold-conjugated antibody. Our study shows that not only morphology but also antigenic phenotype of lymphatics differs significantly from blood vessels.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 8592064 [PubMed - indexed for MEDLINE]

11: J Acquir Immune Defic Syndr Hum Retrovirol. 1995 Nov;10(3):295-305.

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Heterogeneity of spindle cells in Kaposi's sarcoma: comparison of cells in lesions and in culture.

Kaaya EE, Parravicini C, Ordonez C, Gendelman R, Berti E.

Gallo RC, Biberfeld P.

Immunopathology Laboratory, Karolinska Institute, Stockholm, Sweden.

The immunophenotype of spindle cells in epidemic, endemic, and classic (sporadic) Kaposi's sarcoma (KS) lesions was defined by the demonstration of various cell markers and compared with that of KS-derived cell lines. No significant histological or immunophenotypic differences were observed between the three clinical types of KS at comparable stages. The spindle-cell compartment of the different KS types was composed predominantly of a mixture of proliferating CD45+/CD68+ bone-marrow-derived monocytes and TE7+/collagen+ fibroblastic cells with varying expression of EN4/PAL-E/CD31/CD34/CD36 endothelial-associated antigens and/or smooth-muscle-specific alpha-actin (alpha-actin). The latter cells appeared to represent transitional forms of fibroendothelial and fibromyocytic cells. The in vitro cultured KS-derived cell lines (KS-3, KS-6, and KS-8) expressed the fibroblastic antigen TE7 and smooth-muscle-specific alpha-actin but not leukocytic or endothelial-associated antigens consistent with the phenotype of fibromyoid spindle cells of primary lesions. Neither HIV antigen nor provirus DNA was demonstrable in the epidemic KS lesions. The observed heterogeneity of the spindle-cell compartment further substantiates the view that Kaposi's sarcoma, irrespective of clinical setting, expresses salient features more compatible with reactive, tumor-like lesion than clonal sarcoma.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 7552491 [PubMed - indexed for MEDLINE]

12: Circulation. 1995 Sep 15;92(6):1494-8.

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Chronic congestive heart failure is associated with a phenotypic shift of intramyocardial endothelial cells.

Marijanowski MM, van Laar M, Bras J, Becker AE.

Department of Cardiovascular Pathology, University of Amsterdam, The Netherlands.

BACKGROUND: There is evidence that patients with chronic congestive heart failure have endothelial cell-related abnormalities of the peripheral circulation and the coronary microvasculature. For that reason, we have studied the phenotypic expression of endothelial cells in hearts of patients with congestive heart failure. **METHODS AND**

RESULTS: We studied cardiac explants ($n = 19$) and autopsy hearts ($n = 5$) of patients with chronic congestive heart failure caused by either a dilated cardiomyopathy ($n = 12$) or ischemic heart disease ($n = 12$) and compared them with normal hearts ($n = 12$). The antigenic expression obtained with several endothelial cell markers (factor VIII-related antigen, EN-4, Ulex europaeus agglutinin-1 (UEA-1), PAL-E, endoglin, and endothelin) and adhesion molecules (intercellular adhesion molecule [ICAM], vascular cell adhesion molecule [VCAM], or E-selectin) was compared by use of immunohistochemical techniques. On the basis of the initial findings, the number of PAL-E- and EN-4-positive vessels was counted. The incidence of PAL-E-positive vessels per area was quantified and related to the percentage of heart muscle cells and the total number of vessels per area. In control hearts, endothelial cells rarely were positive for PAL-E. In hearts of patients with ischemic cardiomyopathies, there was distinct staining with this marker. Hearts of patients with dilated cardiomyopathies showed a marked increase in the number of PAL-E-positive endothelial cells. Vessels with a muscular media were PAL-E-negative. Two-sample analysis revealed a statistically significant difference between hearts with dilated cardiomyopathies and ischemic cardiomyopathies ($P < .01$), between hearts with dilated cardiomyopathies and control hearts ($P < .01$), and between hearts with ischemic cardiomyopathies and control hearts ($P < .01$). Endoglin and ICAM were positive but nondiscriminating. Endothelin, VCAM, and E-selectin were negative. **CONCLUSIONS:** A phenotypic shift in endothelial antigen expression of the coronary microvasculature occurs in both ischemic hearts and hearts with dilated cardiomyopathies, as revealed by PAL-E, compared with control hearts. The change may relate to compensatory mechanisms in long-standing chronic heart failure.

PMID: 7664432 [PubMed - indexed for MEDLINE]

□ 13: J Pathol. 1995 Jul;176(3):279-87.

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VWF release and platelet aggregation in human melanoma after perfusion with TNF alpha.

Renard N, Nooijen PT, Schalkwijk L, De Waal RM, Eggermont AM, Liénard D, Kroon BB, Lejeune FJ, Ruiter DJ.

Department of Pathologic Anatomy, Jules Bordet Institute, University of Brussels, Belgium.

Twenty-nine stage IIIA/B melanoma patients treated by isolated limb perfusion (ILP) with a high dose of recombinant human tumour necrosis factor alpha (rHuTNF alpha), interferon gamma (IFN gamma), and melphalan were histologically documented with emphasis on therapy-induced changes of the tumour vasculature.

treatment to compare the morphological change. In order to visualize microvascular changes, immunostaining was performed for von Willebrand factor (VWF), type IV collagen, alpha-smooth muscle actin, endothelial antigen PAL-E, tissue factor, CD41 (thrombocyte marker), and fibrin. In biopsies prior to perfusion, necrosis, haemorrhage, and fibrin thrombi were not found. Within 3 h following triple combination therapy, a change in the distribution of VWF staining occurred, from a discrete endothelial pattern in the untreated lesions to a fuzzy perivascular and subepidermal pattern in the treated lesions. Within 24 h, this was accompanied by intravascular thrombocyte aggregation and erythrostasis, in the absence of tissue factor and fibrin deposits. These findings indicate that the thrombocyte aggregation observed is not caused by local procoagulant activity, but is rather the result of the therapy-associated vascular damage or haemostasis. Although it is difficult to derive the dynamics of this process from static images, we assume that TNF alpha induced endothelial cell damage, leading to VWF release. Release VWF may play a role in the adhesion between thrombocytes and the damaged endothelium or the denuded subendothelium. As a consequence, the blood flow is impaired, leading to congestion and oedema, compatible with an early stage of haemorrhagic infarction.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 7674090 [PubMed - indexed for MEDLINE]

□ 14: Exp Nephrol. 1994 Nov-Dec;2(6):324-44.

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Evaluation of nephrotoxicity in vitro using a suspension of highly purified porcine proximal tubular cells and characterization of the cells in primary culture.

Kruidering M, Maasdam DH, Prins FA, de Heer E, Mulder GJ,
Nagelkerke JF.

Leiden/Amsterdam Center for Drug Research, Division of Toxicology,
The Netherlands.

Proximal tubular cells (PTC) were isolated from porcine kidney by collagenase treatment, subsequently purified on a discontinuous density gradient and finally cultured. Porcine PTC (PPTC) in primary culture expressed keratin, characteristics of epithelia and brush border specific glycoproteins (FX1A). In addition, vimentin was present. All cells were negative for the endothelial marker pal-E. Less than 0.1% expressed the Tamm-Horsfall protein, characteristic of the distal tubule, while less than 0.3% of all cells in culture expressed desmin, characteristic of connective tissue (i.e. fibroblasts) and mesangial cells. Ultrastructural analysis revealed microvilli, tight junctions and

abundant mitochondrial and lysosomes, all characteristics of proximal tubular cells. Freshly isolated PPTC were validated as in vitro model to detect nephrotoxicity by studying the effect of mercuric chloride, cis-platin, p-aminophenol and the halogenated alkenes 1,2 dichlorovinyl-l-cysteine, S-(1,1-difluoro-2,2-dichloroethyl)-L-cysteine (DCDFE-cys) and the glutathione conjugate of DCDFE on viability and mitochondrial membrane potential. The cells responded, time- and dose-dependently, to the nephrotoxic compounds with a decrease in mitochondrial membrane potential and loss of viability. The sensitivity of the porcine cells in detecting toxic effects corresponded favorably with in vitro systems derived from other animals.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 7859034 [PubMed - indexed for MEDLINE]

 15: Behring Inst Mitt. 1993 Aug;(92):258-72.

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Angiogenesis in wound healing and tumor metastasis.

Ruiter DJ, Schlingemann RO, Westphal JR, Denijn M, Rietveld FJ, De Waal RM.

Department of Pathology, University Hospital Nijmegen St. Radboud, The Netherlands.

Formation of new blood vessels is essential for several physiological and pathological events, e.g. embryogenesis, wound healing and tumor growth and metastasis. In order to increase the insight into the mechanisms of angiogenesis we have visualized the different components of the microvasculature in human wounds and tumors by immunohistochemistry on the light and electronmicroscopic level. For this purpose, antibodies recognizing distinct markers for human endothelial cells, pericytes and basal lamina were used on freshly frozen or paraformaldehyde-fixed tissue samples. In terms of efficacy, the PAL-E antigen is highly specific for blood vessel endothelium. Its sensitivity is less than other endothelial markers, such as von Willebrand factor and CD 31, as it is not expressed in arterioles. Within the context of the microvasculature alpha-smooth muscle actin and the HMW-MAA chondroitin sulphate proteoglycan are useful markers for pericytes. Type IV Collagen and Laminin can be visualized consistently in the microvascular basal lamina. During the formation of granulation tissue in wound healing a heterogeneity of the expression of endothelial and pericyte markers is found. In the least matured zone in granulation tissue of decubitus lesions and experimental skin wounds microvessels already contained both endothelial cells and pericytes, suggesting a role for both cell types in the early steps of angiogenesis. Regarding the tumor microvasculature,

that did show expression of the other endothelial markers studied. Broad staining in pericytes was found for the HMW-MAA chondroitin sulphate proteoglycan. In contrast, these cells only locally expressed alpha-smooth muscle actin. Staining of the basal lamina components Type IV Collagen and Laminin within tumors was not restricted to the microvasculature. Therefore, antibodies recognizing endothelial markers, particularly PAL-E and BMA 120, are preferable as tools to visualize the tumor microvasculature. In accordance with the situation in granulation tissue of wound healing the broad presence of pericytes in the microvasculature of human tumor suggests an involvement of this cell type in tumor angiogenesis. Recent immunohistochemical studies on human tumor lesions indicated that a high number of microvessels adjacent to the tumor as a measure of tumor angiogenesis is an unfavorable prognostic factor in cutaneous melanoma, mammary carcinoma and non-small cell pulmonary carcinoma. This new application of immunohistochemistry represents a valuable, clinically relevant adjunct to the repertoire of the surgical pathologist.

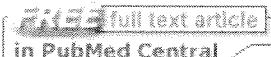
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- Research Support, Non-U.S. Gov't
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PMID: 7504453 [PubMed - indexed for MEDLINE]

□ 16: Am J Pathol. 1993 Jul;143(1):105-20.

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Defect of Fc receptors and phenotypical changes in sinusoidal endothelial cells in human liver cirrhosis.

Muro H, Shirasawa H, Kosugi I, Nakamura S.

Department of Pathology, Hamamatsu University School of Medicine, Japan.

To analyze the pathological changes occurring in Fc receptors (FcRs) in sinusoidal endothelial cells (SECs) in chronic liver diseases, we first characterized immunohistochemically the SEC FcRs by using monoclonal antibodies (MAbs) to FcRs and then investigated the distribution of the SEC FcRs by using peroxidase-antiperoxidase IgG complexes as a ligand on frozen sections. MAb 2E1 to FcRII reacted with SECs in a similar manner to peroxidase-antiperoxidase IgG and blocked the peroxidase-antiperoxidase IgG binding to SECs, whereas MAbs 3G8 and Leu-11b to FcRIII did not. FcRs in normal liver were found along the sinusoidal walls, except for those in the outer periportal zones, but FcRs in chronic active hepatitis and cirrhosis were intermittently or focally absent. The lengths of the FcR-positive portion of sinusoids in unit areas were respectively about 54% and 76% of the normal values in active and inactive cirrhosis. Where FcRs

were absent, the MAbs CD36, CD31, and EN4 revealed the presence of sinusoids and, in active cirrhosis, frequently the thickening of liver cell plates. The FcR-negative SECs in the outer periportal zones of normal livers were different from the SECs of other sites in the presence of PAL-E antigen and a rich amount of EN4 antigen, though these sinusoids possessed Kupffer cells and no perisinusoidal deposition of laminin. The FcR-negative SECs in liver diseases occasionally presented the character of ordinary blood vessels, viz., PAL-E antigen, CD34 antigen, and a deficiency of Kupffer cells, regardless of perisinusoidal laminin deposition. However, they preserved the character of normally FcR-possessing SECs, viz., CD36 antigen, and a small amount of EN4 and CD31 antigens. These findings indicate that the outer-periportal SECs in normal livers are phenotypically different from other SECs and that the SECs in diseased livers frequently undergo phenotypical changes, including loss of FcRs, regardless of perisinusoidal laminin deposition, i.e., capillarization of the sinusoids. These phenotypical changes in SECs may reduce the capacity of FcR-mediated IgG-IC metabolism in diseased livers.

PMID: 7686339 [PubMed - indexed for MEDLINE]

PMCID: PMC1886954

17: Blood. 1993 Apr 1;81(7):1726-38.

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Bone marrow stroma in humans: anti-nerve growth factor receptor antibodies selectively stain reticular cells *in vivo* and *in vitro*.

Cattoretti G, Schirò R, Orazi A, Soligo D, Colombo MP.

Divisione di Anatomia Patologica e Citologia, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milano, Italy.

Two anti-nerve growth factor receptor (LNGFR or p75NGFR) antibodies, Me20.4 and Me8211, label stromal cells with dendritic features in fresh smears and in formalin-fixed, paraffin-embedded human bone marrow (BM). The LNGFR+ cells have an oval nucleus, a scanty cytoplasm with long dendrites that intermingle with the hematopoietic cells, line the abluminal side of sinus endothelial cells, and provide the scaffold for the hematopoietic marrow. At the electron microscopy level, the immunogold tag labels the body and the long branching dendrites of fibroblast-like cells with scanty cytoplasm containing mitochondria, endoplasmic reticulum, and dense bodies. The LNGFR+ cells are positive for alkaline phosphatase, reticulin, collagen III, vimentin, TE-7, and CD13 but negative for endothelial (vWF, CD34), neural (CD56, neurofilament) and leukocyte

markers (CD45, CD68). The LNGFR+ stromal cells appear in the fetal BM before the hematopoietic activity begins, originate from the vessel adventitia, and radiate in the Bm cavity. Long-term BM culture (LTBMC) in vitro contain LNGFR+ stromal cells. We document the presence of RNA message for the low- (LNGFR) and the high-affinity NGF receptor (NTRK1) by using RT-PCR on fresh BM aspirate and on LTBMC. BM biopsies from patients with hematologic fibrogenic diseases and in cytokine-treated cancer patients are evaluated for LNGFR+ cells: the amount of stained cells is correlated with the traditional reticulin stain in cases of myelofibrosis, therapy-related myelodysplasia, leukemia, and detected an increase of stromal cells in cytokine-treated patients. The anti-LNGFR antibodies represent a specific membrane marker for the adventitial reticular cells (ARC) of the human marrow and allow precise evaluation and quantitation of this important BM microenvironment component in vivo and in vitro.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 7681701 [PubMed - indexed for MEDLINE]

□ 18: Am J Pathol. 1992 Sep;141(3):673-83.

Related Articles,
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Antigenic heterogeneity of vascular endothelium.

Page C, Rose M, Yacoub M, Pigott R.

Immunology Department, National Heart and Lung Institute, Harefield Hospital, Middlesex, United Kingdom.

The antigenic status of vascular endothelium from different sites of the normal adult and fetal human cardiovascular system was investigated. Tissues included aorta ($n = 9$), pulmonary artery ($n = 8$), coronary artery ($n = 6$), ventricle/atrium ($n = \text{greater than } 10$), lymph node ($n = 2$), fetal whole heart ($n = 3$), and umbilical cord ($n = 7$). Frozen sections were studied using monoclonal antibodies recognizing endothelial markers (EN4, vWF, Pal-E, and 44G4), vascular adhesion molecules (ICAM-1, ELAM, VCAM, and PECAM), the monocyte/endothelial marker (OKM5), and major histocompatibility complex (MHC) molecules (class I and class II). Results demonstrate that capillary endothelium is phenotypically different from endothelial cells (EC) lining large vessels. Capillary EC strongly express MHC classes I and II, ICAM, and OKM5, which are variably weak to undetectable on large vessels. In contrast, the large vessels strongly express vWF and appear to constitutively express ELAM-1. This suggests that the capillary EC may be more efficient at antigen presentation or more susceptible to immune attack in vivo. Interestingly, normal coronary arteries, unlike all other large vessels,

concentrate on comparative functional studies between capillary, coronary, and large vessel EC.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 1519671 [PubMed - indexed for MEDLINE]

PMCID: PMC1886681

 19: Transplantation. 1992 Sep;54(3):451-7.

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Induction of vascular adhesion molecules during rejection of human cardiac allografts.

Taylor PM, Rose ML, Yacoub MH, Pigott R.

Department of Immunology, Harefield Hospital, Middlesex, United Kingdom.

Adhesion of leukocytes to vascular endothelium is a necessary step leading to the migration of cells into underlying tissues. Vascular adhesion molecules regulate this process and may play an important role in graft rejection. Immunocytochemical studies have been used to investigate the expression of vascular adhesion molecules (ICAM-1, PECAM, VCAM-1, and ELAM-1) in normal donor heart ($n = 15$) and myocardial biopsies from heart transplant patients with acute rejection ($n = 15$). Sections were also stained with antibodies against endothelium, leukocytes, MHC antigens, and markers of cell activation. In donor heart EN4, vWF, ICAM-1, PECAM, MHC class I-and, to a lesser extent, VCAM-1 and DR antigen--are expressed on arterioles and venules, whereas ELAM-1 and Pal-E are restricted to venules. Expression of Pal-E, VCAM-1, ICAM-1, and DR antigen was increased during rejection. Capillary endothelium normally expresses EN4, ICAM-1, PECAM, MHC class I, and DR antigen but little, if any, VCAM-1 or ELAM-1. During rejection, however, there is an increased expression of all adhesion molecules. This is paralleled by an increased expression of vWF by capillary endothelium. In addition, ICAM-1 like MHC class I antigen is induced on the myocardial membrane and intercalating discs. Endocardium from donor heart expresses EN4, vWF, PECAM, MHC class I, and sometimes Pal-E and ICAM-1, but very little VCAM-1, ELAM-1 or DR antigen. There is an increased expression of Pal-E, ICAM-1, VCAM-1, and DR antigen on endocardium from rejecting heart biopsies. Proliferating Ki-67+ cells and activated T cells expressing the receptor for IL-2 were also found in biopsies during rejection episodes.

PMID: 1384180 [PubMed - indexed for MEDLINE]



Immune response to the endothelium in myocarditis, dilated cardiomyopathy and rejection after heart transplantation.

Hengstenberg C, Rose ML, Olsen EG, Maisch B.

Department of Internal Medicine-Cardiology, Philipps-University, Germany.

The role of endothelial cells in inflammatory heart disease and rejection after heart transplantation is only partly understood. To determine whether an immune reaction against endothelial cells occurs we examined endomyocardial biopsies from patients with myocarditis ($n = 13$), dilated cardiomyopathy ($n = 23$), no clinical rejection ($n = 10$) and moderate to severe rejection after heart transplantation ($n = 10$). These were compared to 'normal' donor hearts with monoclonal endothelial-specific antibodies EN4, Pal-E and F VIII-related antigen. Nearly all endothelial cells were stained positively with EN4. There were no significant changes in the binding of the antibodies except in rejection when Pal-E and F VIII-related antigen were significantly increased. It is concluded that apart from their possible role as antigen-presenting cells, endothelial cells are important targets in rejection after heart transplantation. Damage or cytolysis of endothelial cells may cause both altered transendothelial permeability and functional decrease in antigen presentation.

PMID: 1915445 [PubMed - indexed for MEDLINE]

21: Eur Heart J. 1991 Aug;12 Suppl D:147-50.

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Immunocytochemical markers of activation in cardiac transplant rejection.

Rose M, Page C, Hengstenberg C, Yacoub M.

Immunology Department, Harefield Hospital, Middlesex, U.K.

Immunocytochemical analysis of endomyocardial biopsies from cardiac transplant patients has defined changes in expression of antigens, expressed on both the myocardium and endothelium which are characteristic of rejection. Biopsies taken from normal donor heart (prior to transplantation) have been compared with biopsies showing histological signs of rejection. There is induction of MHC class I antigen on the normally negative myocardial plasma membrane and induction of the adhesion molecule ICAM-1 on the intercalating discs. Constitutive endothelial cells which constitutively express Class II DR

antigen and ICAM-1 in normal heart show increased of endothelial antigens Pal-E and FVIII-RA during rejection. These results demonstrate perturbation of the endothelial system during rejection and possibly indicate damage to the capillary endothelial cells.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 1680687 [PubMed - indexed for MEDLINE]

 22: J Vasc Surg. 1991 Mar;13(3):373-81.

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Comment in:

- J Vasc Surg. 1992 Feb;15(2):457-9.
- J Vasc Surg. 1992 Mar;15(3):583-5.

Cells derived from omental fat tissue and used for seeding vascular prostheses are not endothelial in origin. A study on the origin of epitheloid cells derived from omentum.

Visser MJ, van Bockel JH, van Muijen GN, van Hinsbergh VW.

Department of Vascular Surgery, University Hospital, Leiden.

The use of microvascular endothelial cells derived from omental tissue has been advocated to seed vascular grafts with autologous endothelial cells in high density. The purpose of our study was to evaluate the precise origin of these cells. Therefore we have compared cellular characteristics of these cells with those of endothelial cells isolated by collagenase treatment of human umbilical veins. The omental cells were isolated from omental tissue from four different patients by incubation in a collagenase-disperse solution. Part of the material was processed by Percoll density gradient centrifugation in an attempt to purify the isolates. Cellular characteristics of both types of cells were determined by studying the morphologic features of the cells and by determining the presence of von Willebrand factor, antigens EN-4 and PAL-E specific for endothelial cells, cytokeratins 8 and 18, vimentin and desmin, and uptake of dil-acetylated low-density lipoprotein. Epitheloid cells from omental tissue, isolated after collagenase treatment and either purified or nonpurified by Percoll density gradient centrifugation, differed from human umbilical vein endothelial cells with respect to the presence of surface microvilli, the expression of von Willebrand factor, EN-4 and PAL-E, and the presence of cytokeratins 8 and 18 and desmin. von Willebrand factor (in a granular staining pattern) and the presence of EN-4 and PAL-E were only detected in human umbilical vein endothelial cells. Vimentin was present in both cell types, whereas cytokeratins 8 and 18 and desmin were only present in cells derived from omentum. From these data we conclude that the isolated microvascular endothelial cells

omentum are not endothelial but mesothelial in nature.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 1999856 [PubMed - indexed for MEDLINE]

 23: Transplantation. 1990 May;49(5):895-9.

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Comment in:

- Transplantation. 1990 Dec;50(6):1083-4.

Immunocytochemical changes suggestive of damage to endothelial cells during rejection of human cardiac allografts.

Hengstenberg C, Rose ML, Page C, Taylor PM, Yacoub MH.

Immunology Department, Harefield Hospital, Middlesex, United Kingdom.

Interest in the endothelium as a possible initiator or target of the antiallograft response prompted the following study. Immunocytochemical techniques have been used to investigate the expression of the endothelial markers EN4, Pal-E, and FVIII-RA in normal human heart, cardiac biopsies from patients with various cardiac diseases (dilated cardiomyopathy [DCM] and myocarditis [MCO]), and cardiac biopsies from heart-transplant recipients undergoing acute rejection or free of rejection. Quantitative data demonstrated greater preponderance of EN4 cells in normal heart than the other markers. In biopsies showing histologic signs of rejection, there was no difference in the number of EN4 positive cells compared to normal. In contrast, there was found a striking increase in the proportion of cells that are Pal-E positive and a significant increase in the proportion of FVIII-RA positive cells in these biopsies. The patient details provided suggest these results do not reflect vascular damage due to cyclosporine but may well reflect damage caused by the rejection process.

PMID: 2186522 [PubMed - indexed for MEDLINE]

 24: Leukemia. 1989 Jan;3(1):61-7.

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A quantitative and dynamic study of endothelial cells and megakaryocytes in human long-term bone marrow cultures.

Berneman ZN, Chen ZZ, Ramael M, Van Poucke K, Korthout M, van Bockstaele DR, Peetermans ME.

Laboratory of Experimental Hematology, University of Antwerp (UIA), Edegem, Belgium.

The quantitative evolution of endothelial cells (ECs) in Dexter-type human long-term bone marrow cultures (HTLBMCs) was investigated. Using monoclonal antibodies directed against von Willebrand factor (vWF) and against membrane antigens (EN-4 and PAL-E), a low percentage--usually less than 1% of stromal cells--of ECs was detected in all confluent cultures established from 11 different bone marrow samples. Generally these cells are not associated directly with the areas of myelopoiesis ("cobblestone areas"). ECs cannot be demonstrated in the adherent layer of most young, non-confluent, and of some old, HTLBMCs. In some instances, morphological features suggestive of dynamic behavior were seen (sprouting, canal formation). In addition, a very low proportion of vWF-positive megakaryocytic cells was found in 4 of 11 cultures, always in direct contact with the stromal fibroblastic cells.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 2462657 [PubMed - indexed for MEDLINE]

 25: Lab Invest. 1985 Jan;52(1):71-6.

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Monoclonal antibody PAL-E specific for endothelium.

Schlingemann RO, Dingjan GM, Emeis JJ, Blok J, Warnaar SO, Ruiter DJ.

A monoclonal antibody, PAL-E, is described that is specific for endothelial cells. The monoclonal antibody, an IgG2a, markedly stains endothelium of capillaries, medium-sized and small veins, and venules in frozen sections of human and some animal tissues tested. It reacts not at all or only weakly with endothelium of large, medium-sized, and small arteries, arterioles, and large veins and does not stain the endothelial lining of lymphatic vessels and sinus histiocytes. The cellular staining pattern and tissue staining were different from those obtained with antifactor VIII R:AG antiserum and Ulex europaeus I lectin. Blocking experiments indicated that these three reagents recognize different endothelial binding sites. Therefore, PAL-E is a new staining reagent for endothelium in frozen sections. Based on

immunolectronmicroscopic observations, the antigenic determinant recognized by PAL-E is associated with endothelial vesicles.

PMID: 3880842 [PubMed - indexed for MEDLINE]

26: J Gerontol. 1985 Mar;40(2):172-8.

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A system of classifying leisure activities in terms of the psychological benefits of participation reported by older persons.

Tinsley HE, Teaff JD, Colbs SL, Kaufman N.

The psychological benefits of 18 commonly chosen leisure activities were investigated using the Paragraphs About Leisure-Form E (PAL-E), which measures the psychological benefits of participation in leisure activities. The data were cluster analyzed using Ward's hierarchical grouping procedure, and a conceptual framework was developed for understanding the psychological benefits derived from participation in leisure activities by persons in the 55 to 75 age range. The data support the conclusions that leisure activities may be grouped into meaningful families or clusters on the basis of their psychological benefits.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 3973357 [PubMed - indexed for MEDLINE]

27: J Clin Pathol. 1986 Jul;39(7):742-9.

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Histogenesis of Kaposi's sarcoma in patients with and without acquired immune deficiency syndrome (AIDS).

Jones RR, Spaull J, Spry C, Jones EW.

Immunohistochemical studies were performed in thirty skin biopsies from patients with Kaposi's sarcoma, who did and did not have the acquired immune deficiency syndrome (AIDS). Tumour histogenesis was rigorously tested using a battery of endothelial cell markers, which included two new monoclonal antibodies, EN4 and PAL E. These are both specific for endothelial cells and can be visualised in

appropriately fixed paraffin embedded tissue. Whereas EN4 labels all endothelial cells, PAL E is negative in endothelium of lymphatic derivation. Lectin binding with Ulex europaeus agglutinin 1 (UEA-1) and the presence of factor VIII related antigen (FVIIIR) and laminin were also examined. In nodular lesions of Kaposi's sarcoma the spindle cell areas were positive with EN4 and UEA-1, negative with PAL E, and showed focal staining for FVIIIR and laminin. These results confirm that the tumour is of endothelial cell origin. Six patch stage lesions showed a network of angulated spaces, lined by cells that were positive with EN4 and UEA-1, negative with PAL E and anti-FVIIIR, and showed only weak staining for laminin. This pattern was observed in both AIDS and non-AIDS related cases and strongly favours a lymphatic derivation for the tumour. This has important implications as it suggests that lymphatic endothelium may have special characteristics that lead to neoplastic transformation in patients with retrovirus infection.

PMID: 3090109 [PubMed - indexed for MEDLINE]

PMCID: PMC500035

28: J Immunol Methods. 1986 Jul 11;91(1):45-52.

[Related Articles](#),
[Links](#)

The detection of endothelial cell antigens in cutaneous tissue using methacarn and periodate lysine paraformaldehyde fixation.

Holden CA, Spaull J, Williams R, Spry CJ, Jones RR, Jones EW.

The use of monoclonal antibodies with endothelial cell specificity has prompted a search for methods of fixation which combine the morphology of paraffin-embedded tissue, with preservation of labile membrane antigens. Immunohistochemical staining using a variety of endothelial cell markers was compared in tissue fixed in formalin, methacarn, periodate lysine paraformaldehyde (PLP) and in frozen tissue. Whilst lectin-binding with Ulex europaeus agglutinin I (UEA) and localisation of Factor VIII-related antigen (FVIII RA) and laminin was well-visualised in methacarn-fixed and PLP-fixed tissue, fixation in PLP was necessary for the two monoclonal antibodies, PAL-E and EN4. PLP fixation has considerable potential for investigating the histogenesis of vascular tumours, particularly in Kaposi's sarcoma where frozen tissue represents a biological hazard. The normal staining pattern of human dermal vasculature is described in relation to the above endothelial cell antigens.

PMID: 3014005 [PubMed - indexed for MEDLINE]

29: Histopathology. 1987 Jan;11(1):37-51.

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The histogenesis of angiosarcoma of the face and scalp: an immunohistochemical and ultrastructural study.

Holden CA, Spaul J, Das AK, McKee PH, Jones EW.

Thirteen cases of angiosarcoma of the face and scalp have been examined using immunohistochemistry and electron microscopy. Endothelial cell markers have been employed in an immunoperoxidase technique on tissue that has either been routinely processed, periodate-lysine paraformaldehyde fixed (PLP) and cold processed, or fixed in methacarn. A consistent pattern of endothelial cell labeling was only achieved in the PLP fixed tissue. In this fixative the angiosarcomas were factor VIII related antigen negative, Ulex europaeus lectin positive, laminin positive, unlabelled by the monoclonal antibody PAL-E, and positively labelled by the monoclonal antibody EN4. Ultrastructural examination of four cases showed evidence of vascular lumina in all tumours. Weibel-Palade bodies were seen in only one case but three tumours showed some evidence of tight junction formation and marginal folding. Thus, our cell marker studies can be interpreted as consistent with a lymphatic derivation for this type of angiosarcoma but in contra-distinction the ultrastructural studies showed tumour channels with features suggestive of blood vessel differentiation.

PMID: 3104187 [PubMed - indexed for MEDLINE]

30: Arch Dermatol Res. 1987;279(8):499-503.

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Initial lesions of HIV-related Kaposi's sarcoma--a histological, immunohistochemical, and ultrastructural study.

Schulze HJ, Rütten A, Mahrle G, Steigleder GK.

Department of Dermatology, University of Cologne, Federal Republic of Germany.

Kaposi's sarcoma (KS) in human immunodeficiency virus infection (HIV) has become a rather frequent manifestation of the previously rare disease with fatal outcome. Initial lesions of KS were studied by means of histopathology, immunohistology, and electron microscopy in order to define the earliest alterations. The histopathological changes of initial lesions were distinct, consisting of (1) discrete proliferation of capillary vessels, (2) dissection of collagen by proliferating spindle cells which formed slits, (3) atypical spindle cells arranged in an Indian file pattern, and (4) the lack of any inflammatory

cellular infiltrate. Double staining with antibodies against vimentin and immunohistochemical markers for endothelial cells revealed that slits forming vimentin-positive spindle cells displayed laminin, factor VIII, and PAL-E. Atypical vimentin-positive spindle cells arranged in an Indian file pattern inconsistently expressed laminin and factor VIII, but not PAL-E. KS cells rarely stained with the lectin UEA I, not even in case of less advanced dedifferentiation. Electron microscopy showed gradual transformation between spindle cells forming slits and those having lost the ability to form incomplete vessel walls. The present findings support the view that KS develops from the endothelial cells of the blood vessels. The proliferation of atypical endothelial cells as early as in initial lesions and the lack of inflammation favors the primary neoplastic genesis of KS.

PMID: 3324975 [PubMed - indexed for MEDLINE]

31: J Oral Pathol. 1988 Sep;17(8):416-20.

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Expression of endothelial cell markers PAL-E and EN-4 and Ia-antigens in Kaposi's sarcoma.

Nadimi H, Saatee S, Armin A, Toto PD.

Loyola University Medical Center, Maywood, Illinois 60153.

Eleven biopsy specimens of Kaposi's sarcoma (KS) removed from the skin and oral mucosa were examined immunohistochemically with monoclonal antibodies PAL-E and EN-4, specific for human vascular endothelial cells, and with LN-3 monoclonal antibody reactive with immune-associated (Ia) antigens in the HLA-DR locus. The early lesions of KS, corresponding to the patch phase, contained hyperplastic venules and an increased number of lymphatic capillaries. The lymphatic capillary endothelium was reactive with EN-4, whereas, PAL-E reacted only with blood vessel endothelial cells. The spindle cells, like lymphatic endothelial cells, were non-reactive with PAL-E but showed positive reaction with EN-4 antibodies. The observed morphologic pattern of vasculogenesis and the demonstrated immune-reactivity in KS support an origin from the venule-lymphatic junction. This is an aberrant pattern but reminiscent of normal embryonal lymphatic channel development. The lymphatic capillaries and vascular slits were nonreactive with LN-3 antibody, but it was positive on cell membranes in a number of spindle cells, suggesting the focal expression of Ia-antigens.

PMID: 3146628 [PubMed - indexed for MEDLINE]

32: J Pathol. 1988 Dec;156(4):319-24.

A monoclonal antibody stains blastemal but not tubular components of Wilms' tumour.

Sarawar SR, Schlingemann RO, Kelsey A, Fleming S, Kumar S.

Clinical Research Laboratories, Christie Hospital, Manchester, U.K.

The monoclonal antibody PAL-E is specific for endothelial cells in a wide variety of normal and tumour tissue. In normal kidney, PAL-E reacts exclusively with the endothelium of non-glomerular blood vessels. In Wilms' tumour, binding of PAL-E was not restricted to the endothelium; staining of blastemal cells was observed in seven out of eight cases examined. Mesenchymal and tubular components, if present in Wilms' tumour, were negative. In contrast, a monoclonal antibody to Factor VIII-related antigen (RFF-8-R-1) bound only to endothelial cells in these tumours. In fetal kidney, PAL-E binding showed a wider distribution than in adult kidney and both stromal and glomerular capillaries were stained. Tubules and non-endothelial stromal cells were negative. These results indicate that the reactivity of the monoclonal antibody, PAL-E, is not restricted to cells of endothelial origin in all tissues. The implications of these findings for the differentiation of Wilms' tumour are discussed.

PMID: 2852240 [PubMed - indexed for MEDLINE]

33: J Invest Dermatol. 1989 Aug;93(2 Suppl):25S-32S.

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Monoclonal antibody-defined human endothelial antigens as vascular markers.

Ruiter DJ, Schlingemann RO, Rietveld FJ, de Waal RM.

Department of Pathology, University Hospital Nijmegen, The Netherlands.

A review is given of human endothelial antigens recognized by monoclonal antibodies and used as vascular markers. These antigens can be classified tentatively into two categories that partly overlap: 1) differentiation markers and 2) antigens involved in specific cellular functions. Monoclonal antibodies recognizing endothelial differentiation markers reacting with all types of human endothelium can be regarded as constitutive endothelial markers. Other differentiation markers have a restricted distribution that is associated with a subtype of endothelium. Although sensitivity of the markers is high in general, specificity for endothelium is not absolute, based on distribution studies in tissues or in cell lines. With the exception of PAL-E and EN-3/EN-4, it is not clear from the literature whether the antibodies also react with lymphatic endothelium.

Immunohistochemical examination of other species indicate that only BW 200 is restricted to humans. Immunoelectron microscopy of microvascular cells in tissue specimens has revealed that the monoclonal antibodies recognizing differentiation antigens show different subcellular distribution patterns. PAL-E and BW 200 react with the luminal endothelial surface, in a local and diffuse pattern, respectively. Anti-Von Willebrand factor (i.e., Factor VIII-related ag) antibodies react with Weibel-Palade bodies but also with subendothelial structures. Applications of immunohistochemistry using monoclonal antibodies in diagnostic pathology include assessment of vascular invasion by cancer cells, and identification of endothelial neoplasms and related disorders. Because anti-Factor VIII-related antigen and BW 200 are applicable on formaldehyde-fixed and paraplast-embedded tissue, they are most suitable for histodiagnostic application. Immunohistochemistry using monoclonal antibodies recognizing endothelial antigens involved in specific cellular functions also may contribute to pathobiologic research on the characterization of blood-tissue barriers, e.g., in the tumor vascular bed.

Publication Types:

- Research Support, Non-U.S. Gov't
- [Review](#)

PMID: 2666520 [PubMed - indexed for MEDLINE]

 34: Lancet. 1990 Mar 17;335(8690):671.

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PAL-E, monoclonal antibody with immunoreactivity for endothelium specific to brain tumours.

[Leenstra S, Das PK, Troost D, Bosch DA, Claessen N, Becker AE.](#)

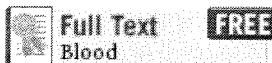
Publication Types:

- Letter

PMID: 1969053 [PubMed - indexed for MEDLINE]

 35: Blood. 1990 Apr 1;75(7):1490-7.

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Characterization and fibrinolytic properties of human omental tissue mesothelial cells. Comparison with endothelial cells.

van Hinsbergh VW, Kooistra T, Scheffer MA, Hajo van Bockel J, van Muijen GN.

Gaubius Institute TNO, Leiden, The Netherlands.

It has been reported that omental fat tissue is a good source of human microvascular endothelial cells. By characterization we demonstrate that the epitheloid cells isolated from omental tissue are not endothelial cells, but mesothelial cells. They contain abundant cytokeratins 8 and 18, which are absent in endothelial cells, and vimentin. No staining with the endothelial-specific antibodies EN-4 and PAL-E is observed. A faint and diffuse staining of von Willebrand factor (vWF) is seen in mesothelial cells, whereas microvascular endothelial cells from subcutaneous fat display vWF in distinct granular structures. Human peritoneal mesothelium produces plasminogen activator-dependent fibrinolytic activity, which is essential in the resolution of fibrous exudates and may therefore be important in preventing the formation of fibrous peritoneal adhesions. This fibrinolytic activity is plasminogen activator-dependent, but has not been fully characterized. We report here that human omental tissue mesothelial cells in vitro produce large amounts of tissue-type plasminogen activator (t-PA), together with type 1 and 2 plasminogen activator inhibitor (PAI-1 and PAI-2). PAI-1 is predominantly secreted into the culture medium, whereas the major part of PAI-2 is found in the cells. No urokinase-type plasminogen activator is detected. On stimulation with the inflammatory mediator tumor necrosis factor (TNF), at least a threefold decrease in t-PA antigen is observed, together with an increase in both PAI-1 and PAI-2. TNF also induces a marked change in cell shape. Whereas TNF and bacterial lipopolysaccharide (LPS) have similar effects on the production of PA inhibitor by human endothelial cells, LPS has no or only a relatively small effect on the fibrinolytic properties of mesothelial cells. The decreased fibrinolytic activity induced by the cytokine TNF may impair the natural dissolution of fibrin deposits at the peritoneum in the presence of an inflammatory reaction.

PMID: 2107884 [PubMed - indexed for MEDLINE]

36: Lab Invest. 1990 Dec;63(6):841-52.

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Identification of endothelial and mesothelial cells in human omental tissue and in omentum-derived cultured cells by specific cell markers.

Pötzsch B, Grulich-Henn J, Rössing R, Wille D, Müller-Berghaus G.

Clinical Research Unit for Blood Coagulation and Thrombosis, Max-Planck-Gesellschaft, Giessen, West Germany.

Human omental tissue has been used as a source for the isolation and cultivation of microvascular endothelial cells, but also for mesothelial cells. Since both cell types have several morphologic and functional features in common, concerns were raised whether endothelial cells can be separated from mesothelial cells by the methods described for the isolation of microvascular endothelial cells. In the present study, endothelial cells were identified in the capillaries of native human omentum by several endothelial-cell specific markers. von Willebrand factor was demonstrated by polyclonal and monoclonal antibodies, a lectin-specific ligand by *Ulex europaeus I*, and an endothelial-cell specific surface epitope by the monoclonal antibody, PAL-E. These markers were not found positive with mesothelial cells of native omentum. Mesothelial cells were identified by monoclonal antibodies against the intermediate filaments, cytokeratin and vimentin. After having demonstrated the specificity of the methods for the distinction between endothelial and mesothelial cells within native omentum, these methods were applied to omentum-derived cells previously claimed to be microvascular endothelial cells. These cultured cells proved to be negative for von Willebrand factor, *Ulex europaeus I* ligand and PAL-E epitope. In contrast to this, the cultivated cells stained positive to cytokeratin and vimentin. Furthermore, it was shown by immunoprecipitation studies that omentum-derived cells did not synthesize and secrete vWF, indicating the nonendothelial nature of these cells. Finally, electron microscopy demonstrated microvilli on the surface of cultivated omentum-derived cells indicative for the mesothelial origin of these cells. The data presented demonstrate that the cells obtained using the previously published methods for the isolation and cultivation of "microvascular endothelial cells" from omental tissue are of mesothelial and not of endothelial origin. Thus, a great number of data obtained with this type of omentum-derived cells thought to be microvascular endothelial cells need re-evaluation.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 1701509 [PubMed - indexed for MEDLINE]

 37: *Rheumatol Int.* 1991;11(4-5):151-5.

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Demonstration of lymphatics in human synovial tissue.

Wilkinson LS, Edwards JC.

Department of Rheumatology Research, University College and Middlesex School of Medicine, London, UK.

Using a cocktail of monoclonal antibodies PAL-E and DE-U-10 (anti-desmin), combined in double labelling techniques with the lectin *Ulex*

were demonstrated in normal human synovial tissue. These vessels were negative for the monoclonal cocktail and positive for UEAI, were thin-walled and were located close to deep arterioles and venules as expected. Elastin was not found to assist identification of lymphatics in synovium. In rheumatoid arthritic synovium no vessels staining in the manner of normal lymphatics were found. This may indicate absence or change of phenotype of this type of endothelium in disease.

PMID: 1784883 [PubMed - indexed for MEDLINE]

 **38:** Gastroenterol Jpn. 1991 Jun;26(3):336-43.

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Histochemical properties of vascular and sinusoidal endothelial cells in liver diseases.

Hattori M, Fukuda Y, Imoto M, Koyama Y, Nakano I, Urano F.

Second Department of Internal Medicine, Nagoya University School of Medicine, Japan.

Liver biopsy specimens with or without liver diseases were examined immunohistochemically to determine the distribution of endothelial cell markers, factor VIII-related antigen (FVIII-RAg), Ulex europaeus agglutinin I (UEA-I) lectin and PAL-E. We also investigated the localization of laminin, a component of the basement membrane. In normal livers, FVIII-RAg, UEA-I and laminin were negative in sinusoidal endothelial cells, but positive in blood vascular endothelia of the portal area. The antigen detected by PAL-E was distributed in venous endothelial cells. PAL-E did not label endothelial cells of the artery. In the lobule, immunoreactivity with PAL-E was weakly detected only in some sinusoids of the periportal area. In chronic active hepatitis and liver cirrhosis, FVIII-RAg and UEA-I stained endothelial cells of neovasculatures in the enlarged portal areas of the fibrous septum surrounding pseudolobules. Some sinusoidal endothelial cells in cirrhotic livers were reactive to UEA-I and FVIII-RAg, whereas PAL-E-positive cells were found rarely in the pseudolobules. In carcinomatous sinusoidal endothelial cells, FVIII-RAg, UEA-I and PAL-E were strongly stained. Laminin underlay these carcinomatous sinusoids. These suggest capillarization of sinusoids in hepatocellular carcinoma. The histochemical approach using endothelial cell markers could be a practical tool in the diagnosis of hepatocellular carcinoma.

PMID: 1653746 [PubMed - indexed for MEDLINE]

 **39:** Am J Pathol. 1991 Jun;138(6):1335-47.

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Differential expression of markers for endothelial cells, pericytes, and basal lamina in the microvasculature of tumors and granulation tissue.

Schlingemann RO, Rietveld FJ, Kwaspen F, van de Kerkhof PC, de Waal RM, Ruiter DJ.

Department of Pathology, Nijmegen University Cancer Center, The Netherlands.

The structure and function of the tumor microvasculature is of great interest for cancer biology, diagnosis, and therapy. The distribution of endothelial cells, pericytes, and basal lamina in tumors is not well documented. In this study, the authors investigated the distribution of markers for these different components in a series of malignant human tumors and in human granulation tissue, both situations with extensive angiogenesis. Their results show a striking heterogeneity in the expression of markers for pericytes and endothelial cells between different tumors, but also within a single tumor lesion. To be able to distinguish between these two adjacent cell types decisively, all marker studies were carried out both on the light and the electron microscopical level and compared with staining results in granulation tissue of cutaneous wounds in healthy volunteers and of decubitus lesions. In granulation tissue of decubitus lesions, well-defined zones with increasing levels of maturation can be delineated. It was found that antibodies recognizing von Willebrand factor often failed to stain the tumor capillaries. Of the pericyte markers, alpha-smooth muscle actin was only locally expressed by pericytes in the tumor vasculature, whereas the high-molecular-weight melanoma-associated antigen, a chondroitin sulfate proteoglycan, stained the microvasculature broadly. Staining of the basal lamina components collagen type IV and laminin was, within the tumor, not restricted to the microvasculature. From their findings the authors conclude that 1) for the visualization of the tumor vasculature, antibodies recognizing endothelial markers, especially monoclonal antibodies PAL-E and BMA 120, are preferable to those recognizing pericytes or basal lamina; 2) within the microvasculature of tumors and granulation tissue, a heterogeneity of expression of endothelial and pericyte markers is observed; 3) during the formation of granulation tissue, all three microvascular components can be demonstrated already in the histologically earliest stage, suggesting not only an involvement of endothelial cells but also of pericytes and basal lamina in the initial steps of angiogenesis in wound healing.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 1711288 [PubMed - indexed for MEDLINE]

PMCID: PMC1886404

Endothelial heterogeneity and the acquired immunodeficiency syndrome: a paradigm for the pathogenesis of vascular disorders.

Goerdt S, Sorg C.

Institut für Experimentelle Dermatologie, Westfälischen Wilhelms-Universität Münster.

Vascular disorders comprise a wide range of diverse disease entities. Correspondingly, vessels, and even more so the endothelial which line them, show a remarkable extent of heterogeneous differentiation, e.g. between the blood vascular and lymphatic systems, along the length of the vascular trees, and in the microvascular beds of various organs. The most important morphologic criterion to discriminate between endothelia is continuity (continuous endothelial cell layer and well-formed basement membrane) versus discontinuity (intra- or intercellular gaps and/or reduced or missing basement membrane). Most blood vascular endothelia are of the continuous type, while most sinusoidal and lymphatic endothelia are discontinuous by these criteria. Antigen expression corroborates these morphologic data in that CD31, CD34, and 1F10 antigen are exclusively expressed in continuous endothelia, while MS-1 antigen is preferentially expressed in non-continuous sinusoidal endothelia. In contrast, no specific marker has as yet been described for lymphatic endothelia. Endothelial heterogeneity substantially contributes to the pathogenesis of vascular disorders. For example, in patients with acquired immunodeficiency syndrome the same infectious agent may cause either bacillary angiomatosis (a lobular capillary proliferation) or peliosis (sinusoidal dilatation, endothelial denudation, and development of blood-filled cysts) depending on whether the affected organs have predominantly continuous endothelia or noncontinuous sinusoidal endothelia. Moreover, in Kaposi's sarcoma, it is still an open question of whether the lesion is derived from blood vascular or lymphatic endothelia (Kaposi's sarcoma cells *in situ* do not express the von Willebrand factor+, PAL-E+, 1F10+ phenotype of mature, resting blood vascular endothelia). It is also unresolved how endothelia of either type may be differentially induced to dedifferentiate and how they are recruited into the lesion. Clearly, knowledge about endothelial heterogeneity is still too incomplete to identify the actual mechanisms and molecules that govern the pathogenesis of vascular disorders (including still others than those mentioned here such as atherosclerosis, diabetic angiopathy, and rheumatoid arthritis) affecting distinct endothelia. Further efforts in antigenic phenotyping and in cell and molecular biology of heterogeneously differentiated endothelia should be made to improve this state of affairs.

Publication Types:

- Review

PMID: 1600345 [PubMed - indexed for MEDLINE]

HMEC-1: establishment of an immortalized human microvascular endothelial cell line.

Ades EW, Candal FJ, Swerlick RA, George VG, Summers S, Bosse DC, Lawley TJ.

Biological Products Branch, Centers for Disease Control, Atlanta, Georgia.

The study of human microvascular endothelial cells has been limited, because these cells are difficult to isolate in pure culture, are fastidious in their in vitro growth requirements, and have a very limited lifespan. In order to overcome these difficulties, we have transfected human dermal microvascular endothelial cells (HMEC) with a PBR-322-based plasmid containing the coding region for the simian virus 40 A gene product, large T antigen, and succeeded in immortalizing them. These cells, termed CDC/EU.HMEC-1 (HMEC-1), have been passaged 95 times to date and show no signs of senescence, whereas normal microvascular endothelial cells undergo senescence at passages 8-10. HMEC-1 exhibit typical cobblestone morphology when grown in monolayer culture, express and secrete von Willebrand's Factor, take up acetylated low-density lipoprotein, and rapidly form tubes when cultured on matrigel. HMEC-1 grow to densities three to seven times higher than microvascular endothelial cells and require much less stringent growth medium. HMEC-1 will grow in the absence of human serum, whereas microvascular endothelial cells require culture medium supplemented with 30% human serum. These cells express other cell-surface molecules typically associated with endothelial cells, including CD31 and CD36 and epitopes identified by monoclonal antibodies EN4 and PAL-E. They also express the cell adhesion molecules ICAM-1 and CD44 and following stimulation with interferon-gamma express major histocompatibility complex class II antigens. HMEC-1 specifically bind lymphocytes in cell adhesion assays. Thus HMEC-1 is the first immortalized human microvascular endothelial cell line that retains the morphologic, phenotypic, and functional characteristics of normal human microvascular endothelial cells.

PMID: 1361507 [PubMed - indexed for MEDLINE]

42: Microvasc Res. 1993 Jul;46(1):89-102.

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Human lung microvessel endothelial cells: isolation, culture, and characterization.

Hewett PW, Murray JC.

CRC Gray Laboratory, Mount Vernon Hospital, Northwood,

The pulmonary vasculature is of great physiological/pathological significance. We have isolated and cultured microvessel endothelial cells (HuLEC) from lung tissue obtained from lung transplant recipients by modification of published methods. Pure cultures of HuLEC were isolated by mechanical disaggregation of the tissue prior to sequential dispase and trypsin digestion to obtain microvessel fragments. Magnetic beads (Dynabeads) coated with Ulex europaeus agglutinin-1 were then used to enhance the purity of cultures at the first passage. HuLEC formed contact-inhibited "cobblestone" monolayers on gelatin and fibronectin substrates and capillary-like "tubes" on Matrigel and accumulated acetylated low-density lipoprotein. Immunofluorescent characterization of these cells revealed the presence of von Willebrand Factor, angiotensin-converting enzyme, and thrombomodulin and the expression of antigens for the endothelial cell-specific monoclonal antibodies EN4, PAL-E, and H4-7/33. The endothelial origin of these cells was confirmed by the demonstration of the cell adhesion molecules, platelet endothelial cell adhesion molecule-1 (PECAM-1/CD31), and E-selectin (endothelial leukocyte adhesion molecule-1/ELAM-1) upon stimulation with TNF alpha. These cells should provide a useful tool for studying various aspects of pathology and biology of the pulmonary microvasculature in vitro.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 8412855 [PubMed - indexed for MEDLINE]

43: Cell Tissue Res. 1993 Nov;274(2):211-8.

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Immunohistochemical evidence for the heterogeneity of maternal and fetal vascular endothelial cells in human full-term placenta.

Lang I, Hartmann M, Blaschitz A, Dohr G, Skofitsch G, Desoye G.

Department of Obstetrics and Gynecology, University of Graz,
Austria.

The heterogeneity of endothelial cell surface antigen expression was studied in 5 human full-term placentae by means of indirect immunohistochemistry using 9 monoclonal antibodies and by staining with fluorescent-conjugated Ulex europaeus lectin, both of which are widely used endothelial cell markers. (1) A highly specific, homogeneous staining of fetal and maternal placental vessels of all sizes and anatomical regions was observed by the monoclonal antibodies PAL-E, QBEND10 and 1F10. These antibodies were even more specific than Ulex europaeus lectin, factor VIII antibody and von

Willebrand factor antibody, which cross-reacted with some non-endothelial cells and structures. The reactivity of PAL-E, QBEND10 and 1F10 with residual surface cells of the basal plate strongly suggests an endothelial origin of these cells. (2) In contrast to other organs, PAL-E, QBEND10 and HM15/3 strongly stained endothelial cells of the macrovascular system in the human placenta. This might indicate an organ-associated heterogeneity of fetal endothelial cells. (3) Monoclonal antibodies against receptors for transferrin and IgG (Fc gamma RII) labeled the endothelial cells of fetal placental vessels with increasing intensity distal to the insertion of the umbilical cord. The vessels of the umbilical cord itself were unreactive. This might suggest a heterogeneity of macro- and microvascular endothelial cells.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 7505718 [PubMed - indexed for MEDLINE]

 44: Am J Pathol. 1993 Nov;143(5):1377-88.

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Microvascular pericytes express platelet-derived growth factor-beta receptors in human healing wounds and colorectal adenocarcinoma.

Sundberg C, Ljungström M, Lindmark G, Gerdin B, Rubin K.

Department of Medical and Physiological Chemistry, University of Uppsala, Sweden.

The expression of platelet-derived growth factor- beta (PDGF-beta) receptors in the microvasculature of human healing wounds and colorectal adenocarcinoma was investigated. Frozen sections were subjected to double immunofluorescence staining using monoclonal antibodies (MAbs) specific for pericytes (MAb 225.28 recognizing the high-molecular weight-melanoma-associated antigen, expressed by activated pericytes during angiogenesis), endothelial cells (MAb PAL-E), laminin, as well as PDGF-beta receptors (MAb PDGFR-B2) and its ligand PDGF-B chain (MAb PDGF 007). Stained sections were analyzed by computer-aided imaging processing that allowed for a numerical quantification of the degree of colocalization of the investigated antigens. An apparent background colocalization, varying between 23 and 35%, between markers for cells not expected to colocalize was recorded. This background could be due to limitations of camera resolution, to out-of-focus fluorescence, and to interdigitations of the investigated structures. In all six tumor specimens, co-localization of PDGF-beta receptors and PAL-E was not different from the background co-localization, whereas that of PDGF-beta receptors

and high-molecular weight-melanoma-associated antigen was significantly higher with mean values between 57 and 71%. Qualitatively, the same pattern was obtained in the two investigated healing wounds. PDGF-B chain did not co-localize with either PAL-E or high-molecular weight-melanoma-associated antigen, but PDGF-B chain-expressing cells were, however, frequently found juxtaposed to the microvasculature. The expression of PDGF-beta receptors on pericytes in activated microvessels and the presence of PDGF-B chain-expressing cells in close proximity to the microvasculature of healing wounds and colorectal adenocarcinoma is compatible with a role for PDGF in the physiology of the microvasculature in these conditions.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 8238254 [PubMed - indexed for MEDLINE]

PMCID: PMC1887183

 45: Cancer. 1993 Nov 15;72(10):3061-7.

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Endothelial cell marker PAL-E reactivity in brain tumor, developing brain, and brain disease.

Leenstra S, Troost D, Das PK, Claessen N, Becker AE, Bosch DA.

Department of Neurosurgery, University of Amsterdam, The Netherlands.

BACKGROUND. The endothelial cell marker PAL-E is not reactive to vessels in the normal brain. The present study concerns the PAL-E reactivity in brain tumors in contrast to normal brain and nonneoplastic brain disease. **METHODS.** A total of 122 specimens were examined: brain tumors ($n = 94$), nonneoplastic brain disease ($n = 19$), normal brain ($n = 8$), and fetal brain ($n = 1$). Standard immunohistochemical procedures using a panel of endothelial cell markers were applied to detect vessels reactive to PAL-E. **RESULTS.** PAL-E reactivity to endothelial cells was found in all cases of glioblastoma multiforme, in 75% of the cases of anaplastic astrocytoma, and in 46% of the cases of astrocytoma. Furthermore, PAL-E reactivity was present in diseases with a developmental etiology, such as primitive tumors and congenital vascular malformations. The developing human brain (6-weeks' gestation age) and special sites of the mature brain, sites without blood-brain barrier, showed a strong reactivity, which indicates a relation with the status of blood-brain barrier development. **CONCLUSIONS.** PAL-E is the only marker out of a panel of endothelial cell markers that shows no reactivity to endothelial cells in the normal brain with an intact blood-brain barrier. In primary and metastatic brain tumors, PAL-E is reactive to endothelial cells, except

reactivity in brain tumors most likely is related to angiogenesis and to blood-tumor barrier properties not present in the normal blood-brain barrier.

PMID: 8221574 [PubMed - indexed for MEDLINE]

46: Arch Dermatol. 1994 Jul;130(7):879-83.

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Immunohistochemistry of port-wine stains and normal skin with endothelium-specific antibodies PAL-E, anti-ICAM-1, anti-ELAM-1, and anti-factor VIIIrAg.

Neumann R, Leonhartsberger H, Knobler R, Höningmann H.

Department of Dermatology, University of Vienna Medical School, Austria.

BACKGROUND AND DESIGN: Immunohistochemical analysis using four monoclonal antibodies specific for endothelium was performed to evaluate the possible role the endothelium may play in the pathogenesis of port-wine stains. In 11 patients with port-wine stains, biopsy specimens were obtained from involved and normal skin. On frozen tissue sections, we studied and compared the distribution and staining pattern of PAL-E, anti-intercellular adhesion molecule-1 (ICAM-1), anti-endothelial leukocyte adhesion molecule-1 (ELAM-1), and anti-factor VIIIrAg (FVIIIrAg), all recognizing specific epitopes of vascular endothelial cells. **RESULTS:** The PAL-E, anti-FVIIIrAg, and anti-ICAM-1 antibodies showed a similar distribution and staining pattern. The intensity of staining was equally strong with PAL-E and FVIIIrAg, while the expression of ICAM-1 was moderate. The ELAM-1 antibody exhibited only a weak expression in about 70% of evaluated specimens. No substantial differences in the intensity and distribution pattern of expression of these proteins could be demonstrated between normal skin and port-wine stains. **CONCLUSION:** Our findings suggest that the abnormal vessel pathologic findings in port-wine stains are not due to defects associated with the endothelium. According to PAL-E antibody staining properties, port-wine stain vessels could be classified as capillaries and/or postcapillary venules and small veins.

PMID: 7517655 [PubMed - indexed for MEDLINE]

47: Am J Dermatopathol. 1995 Apr;17(2):131-8.

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[Links](#)

Monophasic cellular variant of infantile myofibromatosis. An unusual histopathologic pattern in two siblings.

Zelger BW, Calonje E, Sepp N, Fink FM, Zelger BG, Schmid KW.

Department of Dermatology, University of Innsbruck, Austria.

Infantile myofibromatosis (IMF) is a distinct clinicopathologic entity characterized by solitary or multicentric tumors present at birth or in early infancy with a typical biphasic (central hemangiopericytoma-like, peripheral leiomyoma-like) histologic pattern. We present a case of IMF in two siblings with onset of disease in late childhood.

Histology of the primary as well as several later tumors was characterized by a monophasic cellular appearance with a prominence of tiny capillaries initially suggesting an unusual vascular tumor. Diagnosis was established by the development of more characteristic biphasic lesions during the course of disease. Immunocytochemistry (Ulex, factor VIII, JC/70A [CD31], PAL-E, BMA120, EN4, QBEnd10 [CD34], SMS actin) and ultrastructural studies showed no (marked) differences between different types of IMF. The monophasic cellular pattern should be recognized as an unusual histologic manifestation of IMF, in particular in patients outside the classical setting or presentation.

Publication Types:

- Case Reports

PMID: 8600777 [PubMed - indexed for MEDLINE]

■ 48: J Dermatol Sci. 1995 Sep;10(2):103-9.

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Expression of endoglin in psoriatic involved and uninvolved skin.

Rulo HF, Westphal JR, van de Kerkhof PC, de Waal RM, van Vlijmen IM, Ruiter DJ.

Department of Dermatology, University Hospital Nijmegen, The Netherlands.

Endoglin is a glycoprotein with TGF-beta binding capacity and is predominantly expressed on endothelial cells. In psoriasis, TGF-beta has appeared to play a role in the extravasation of peripheral blood mononuclear cells via the endothelium. In order to find out more about the role of endoglin in psoriasis, immunohistochemical staining with PN-E2, a novel anti-endoglin, and of PAL-E, recognizing vascular endothelium, was carried out in psoriatic involved, psoriatic

assessed semi-quantitatively using a five-point scale. In psoriatic involved skin, a high endoglin expression was found. In psoriatic uninvolved skin, however, we found that endoglin expression was significantly decreased compared with normal skin. The relevance of these findings to the pathogenesis of psoriasis is discussed.

PMID: 8534608 [PubMed - indexed for MEDLINE]

 49: Am J Trop Med Hyg. 1995 Dec;53(6):633-8.

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Predominant CD8+ infiltrate in limb biopsies of individuals with filarial lymphedema and elephantiasis.

Freedman DO, Horn TD, Maia e Silva CM, Braga C, Maciel A.

Division of Geographic Medicine, University of Alabama at Birmingham, USA.

In 34 individuals with a spectrum of clinical manifestations of Bancroftian filariasis, we investigated whether immunoperoxidase-stained, random, superficial dermal biopsies could further elucidate the nature of the diffuse damage to superficial lymphatics that had been recently demonstrated by radionuclide lymphoscintigraphy. A total of 78% and 68% of limbs from patients with clinical disease and asymptomatic microfilaremia, respectively, contained EN4+PAL-E-lymphatic vessels that were abnormally dilated. The majority of subjects, regardless of clinical classification, had a CD3+ perivascular but not a perilymphatic infiltrate in tissues and no parasites were present. In contrast to those individuals with asymptomatic infection, a striking predominance of CD8+ T cells was found in the tissue of individuals with clinical disease. Tissue pathology consistent with cutaneous bacterial infection was not observed. The prominent perivenular and pericapillary mononuclear infiltrates likely indicate, in light of current understanding of lymphocyte recirculation, the extravasation of lymphocytes from the vascular circulation into the inflamed filarial tissue.

Publication Types:

- Research Support, U.S. Gov't, P.H.S.

PMID: 8561266 [PubMed - indexed for MEDLINE]

 50: Transplantation. 1995 Dec 27;60(12):1451-7.

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transplanted human hearts.**Torry RJ, Labarrere CA, Torry DS, Holt VJ, Faulk WP.**

Center for Reproduction and Transplantation Immunology, Methodist Hospital of Indiana, Indianapolis 46202, USA.

Vascular endothelial growth factor (VEGF) is an endothelial cell-specific mitogen thought to play an important role in coronary collateral vessel formation. We used immunocytochemistry to determine VEGF expression in biopsies ($n = 283$) of transplanted human hearts ($n = 109$) with and without microvascular fibrin. Measures of vascular fibrin, alpha 2 plasmin-inhibitor (a2PI), macrophages, neutrophils, and serum cardiac troponin T titers were used to evaluate myocardial damage. Antibody to T lymphocytes was used to evaluate cellular rejection, and HLA-DR, ICAM-1, and PAL-E antibodies were used to assess endothelial cell activation and phenotypic changes in the microcirculation. No VEGF immunoreactivity was detected in control donor hearts without fibrin, but the proportion of biopsies demonstrating VEGF immunoreactivity increased significantly in allografts with increasing fibrin and a2PI reactivity ($P = 0.0001$). VEGF immunoreactivity was confined to areas of fibrin deposition and was associated with infiltrates of macrophages and neutrophils ($P < 0.0001$), but not with T cells ($P = 0.10$). Biopsies with fibrin/VEGF reactivity were associated with increased capillary endothelial cell HLA-DR, ICAM-1, and PAL-E reactivity. In a subset of patients, serum cardiac troponin-T values were greater in patients with VEGF-positive ($n = 21$) than VEGF-negative ($n = 19$) biopsies ($P = 0.05$). Nested RT-PCR demonstrated that biopsies with and without fibrin/VEGF immunoreactivities expressed VEGF121, VEGF165, and VEGF189 variants, with VEGF165 being the dominate variant. These results indicate that endogenous VEGF is expressed locally following vascular thrombosis and myocardial cell damage, and that VEGF expression may be related to endothelial cell activation and phenotypic changes found in the microcirculation of cardiac allografts.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 8545873 [PubMed - indexed for MEDLINE]

[51] Lab Invest. 1996 Feb;74(2):452-66.

[Related Articles](#),
[Links](#)**Pericytes as collagen-producing cells in excessive dermal scarring.****Sundberg C, Ivarsson M, Gerdin B, Rubin K.**

Department of Medical and Physiological Chemistry, University

Hospital, Uppsala, Sweden.

Immunohistochemistry and image analysis were performed on sections from excessive dermal scar formation to investigate the potential of pericytes to differentiate into collagen-producing cells. Expression of the prolyl-4-hydroxylase beta-subunit (P-4-H) was used as a marker for collagen synthesis as the distribution of this protein was identical to the distribution of procollagen type I C-propeptide and similar to the distribution of cells expressing pro alpha 1(I) collagen mRNA. Double immunofluorescence stainings using combinations of monoclonal antibodies specific for activated pericytes *in vivo* (high molecular weight-melanoma associated antigen (HMW-MAA)), P-4-H, smooth muscle alpha-actin (SMA), endothelial cells (PAL-E), platelet-derived growth factor (PDGF) beta-receptor, and the integrin alpha 5 subunit were performed. Stained sections were analyzed by computerized image analysis allowing for a quantification of the degree of colocalization between pairs of antigens on the same tissue section. Four different subpopulations of HMW-MAA expressing cells were discerned. The first subpopulation corresponded to intramural pericytes, juxtaposed to the endothelium, that expressed HMW-MAA, SMA, integrin alpha 5 subunit and the PDGF beta-receptor, but not P-4-H. The second subpopulation was partly dissociated from the microvascular wall and exhibited a similar antigen expression except for a decrease in expression of SMA. Cells in the third subpopulation were located in the perivascular space and expressed P-4-H, integrin alpha 5 subunit, the PDGF beta-receptor and, albeit less pronounced, HMW-MAA, but not SMA. The fourth subpopulation expressed integrin alpha 5 subunit, HMW-MAA and the PDGF beta-receptor, no expression of SMA and a strong expression of P-4-H. Moreover, an *in vitro* analysis of cells derived from isolated microvascular fragments from human dermis revealed a similar pattern of phenotypical change. Taken together the data suggest that a population of intramural pericytes migrate into the perivascular space and develop into collagen-synthesizing fibroblasts during fibrosis.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 8780163 [PubMed - indexed for MEDLINE]

52: J Invest Dermatol. 1996 Jun;106(6):1293-9.

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Human cutaneous dendritic cells migrate through dermal lymphatic vessels in a skin organ culture model.

Lukas M, Stössel H, Hefel L, Imamura S, Fritsch P, Sepp NT, Schuler G, Romani N.

Department of Dermatology, Kyoto University, Japan.

The capacity to migrate from peripheral tissues, where antigen is encountered, to lymphoid organs, where the primary immune response is initiated, is crucial to the immunogenic function of dendritic cells (DC). The skin is a suitable tissue to study migration. DC were observed to gather in distinct nonrandom arrays ("cords") in the dermis upon culture of murine whole skin explants. It is assumed that cords represent lymphatic vessels. Using a similar organ culture model with human split-thickness skin explants, we investigated migration pathways in human skin. We made the following observations. 1) Spontaneous emigration of Langerhans cells took place in skin cultured for 1-3 d. Nonrandom distribution patterns of strongly major histocompatibility complex class II-expressing DC (cords) occurred in cultured dermis. A variable, yet high (>50%) percentage of these DC coexpressed the Birbeck granule-associated antigen "Lag." Ultrastructurally, the cells corresponded to mature DC. 2) Electron microscopy proved that the dermal structures harboring the accumulations of DC (i.e., cords) were typical lymph vessels. Moreover, markers for blood endothelia (monoclonal antibody PAL-E, Factor VIII-related antigen) and markers for cords (strong major histocompatibility complex class II expression on nonrandomly arranged, hairy-appearing cells) were expressed in a mutually exclusive pattern. 3) On epidermal sheets we failed to detect gross changes in the levels of expression of adhesion molecules (CD44, CD54/ ICAM-1, E-cadherin) on keratinocytes in the course of the culture period. The reactivity of a part of the DC in the dermal cords with Birbeck granule-specific monoclonal antibody "Lag" suggests that the migratory population is composed of both epidermal Langerhans cells and dermal DC. We conclude that this organ culture model may prove helpful in resolving pathways and mechanisms of DC migration.

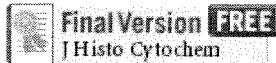
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- Research Support, Non-U.S. Gov't

PMID: 8752673 [PubMed - indexed for MEDLINE]

53: J Histochem Cytochem. 1998 Feb;46(2):165-76.

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Immunoelectron microscopic characterization of human dermal lymphatic microvascular endothelial cells. Differential expression of CD31, CD34, and type IV collagen with lymphatic endothelial cells vs blood capillary endothelial cells in normal human skin, lymphangioma, and hemangioma in situ.

Sauter B, Foedinger D, Sterniczky B, Wolff K, Rappersberger K.

Department of Dermatology, Division of General Dermatology

University of Vienna, Medical School, Vienna, Austria.

We performed a comparative investigation of the immunomorphological characteristics of lymphatic and blood microvascular endothelial cells in normal human skin, cutaneous lymphangiomas, and hemangiomas, employing a pre-embedding immunogold electron microscopic technique. We stained for cell membrane proteins that are commonly used for light microscopic characterization of blood endothelial cells. With blood microvascular endothelial cells, we observed uniform labeling of the luminal cell membranes with monoclonal antibodies (MAbs) JC70 (CD31), EN-4 (CD31), BMA120, PAL-E, and QBEND-10 (CD34), and strong staining of the vascular basal lamina for Type IV collagen under normal and pathological conditions. In contrast, lymphatic microvascular endothelial cells in normal human skin and in lymphangiomas displayed, in addition to a luminal labeling, pronounced expression of CD31 and CD34 along the abluminal cell membranes. Moreover, CD31 was preferentially detected within intercellular junctions. The expression of CD34 was mostly confined to abluminal endothelial microprocesses and was upregulated in lymphangiomas and hemangiomas. Type IV collagen partially formed the luminal lining of initial lymphatics and occasionally formed bridges over interendothelial gaps. Our findings suggest a function of transmigration protein CD31 in recruitment of dendritic cells into the lymphatic vasculature. CD34 labeling may indicate early endothelial cell sprouting. The distribution of Type IV collagen also supports its role as a signal for migration and tube formation for lymphatic endothelial cells.

Publication Types:

- Comparative Study

PMID: 9446823 [PubMed - indexed for MEDLINE]

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